Sprycel

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0086	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	16/06/2022		SmPC	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

II/0083	Submission of the final report from study CA180226 PK substudy, as requested in X/0056/G procedure, and the population PK (PPK) analyses conducted to refine the PK characterization of the dasatinib (BMS-354825) powder for oral suspension (PFOS) in pediatric patients with Philadelphia chromosome positive (Ph+) chronic phase chronic myeloid leukemia (CP-CML) or Ph+ acute lymphoblastic leukemia (ALL). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/04/2022	n/a		
PSUSA/935/202106	Periodic Safety Update EU Single assessment - dasatinib	27/01/2022	22/03/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/935/202106.
IAIN/0085	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	15/03/2022		Annex II and PL	
IAIN/0084	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	14/03/2022		Annex II and PL	
IAIN/0082	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	04/10/2021	n/a		

IA/0080	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	29/06/2021	n/a		
IB/0079	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	10/06/2021	22/03/2022	SmPC	
IB/0077/G	This was an application for a group of variations. B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	05/05/2021	n/a		
IA/0078	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	20/04/2021	22/03/2022	SmPC and PL	
IB/0076	C.I.3.z - Change(s) in the SPC, Labelling or PL	25/02/2021	30/04/2021	SmPC, Annex	

	intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation			II, Labelling and PL	
PSUSA/935/202006	Periodic Safety Update EU Single assessment - dasatinib	14/01/2021	n/a		PRAC Recommendation - maintenance
IA/0074	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	02/09/2020	n/a		
IG/1223/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	17/04/2020	30/04/2021	Annex II and PL	
IG/1193	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/01/2020	n/a		
PSUSA/935/201906	Periodic Safety Update EU Single assessment - dasatinib	16/01/2020	n/a		PRAC Recommendation - maintenance

IA/0071/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	02/10/2019	n/a		
IAIN/0069	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	13/08/2019	n/a		
II/0064	Update of section 5.2 of the SmPC based on results from existing and new pharmacokinetics (PK) analyses together with a review of literature data on the dasatinib PK profile in fasted conditions to assess implications arising for the recommendation for administration, as requested by the CHMP. In addition, the local representative's details for Germany have been updated. Minor editorial changes have been introduced throughout the Product Information. C.I.13 - Other variations not specifically covered	27/06/2019	13/02/2020	SmPC and PL	Dasatinib exposure variability is higher under fasted conditions (47% CV) compared to light-fat meal (39% CV) and high-fat meal (32% CV) conditions. Based on the patient population PK analysis, variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability in bioavailability (44% CV) and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance (30% and 32% CV, respectively). The random inter-occasion variability in exposure is not expected to affect the cumulative exposure and efficacy or safety.

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IAIN/0068	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	29/03/2019	n/a		
PSUSA/935/201806	Periodic Safety Update EU Single assessment - dasatinib	31/01/2019	28/03/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/935/201806.
IB/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/03/2019	n/a		
IG/1059	A.1 - Administrative change - Change in the name and/or address of the MAH	15/02/2019	13/02/2020	SmPC, Labelling and PL	
II/0059	Extension of Indication to include a paediatric indication for Philadelphia chromosome positive acute lymphoblastic leukaemia for Sprycel; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the product information. The RMP version 16.1 has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) -	13/12/2018	06/02/2019	SmPC and PL	Please refer to Scientific Discussion ''Sprycel-H-C-709-II-59''.

	Addition of a new therapeutic indication or modification of an approved one				
IA/0065/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	18/12/2018	n/a		
IAIN/0062	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	07/09/2018	n/a		
IAIN/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/08/2018	06/02/2019	SmPC, Labelling and PL	
X/0056/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/04/2018	02/07/2018	SmPC, Annex II, Labelling and PL	

	Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form				
IG/0889	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	13/02/2018	n/a		
PSUSA/935/201706	Periodic Safety Update EU Single assessment - dasatinib	11/01/2018	n/a		PRAC Recommendation - maintenance
II/0055	Update of section 4.8 of the SmPC in order to add nephrotic syndrome as an adverse reaction based on the results of routine pharmacovigilance activities. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the date of latest renewal (Section 9, SmPC) along with the phone number of the local representative in Croatia and the name of local representative in Ireland listed in the PIL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/06/2017	31/05/2018	SmPC, Labelling and PL	4.8 Undesirable effects Nephrotic syndrome was included as a new adverse reaction with the frequency unknown.
IA/0057	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	24/05/2017	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/935/201606	Periodic Safety Update EU Single assessment - dasatinib	12/01/2017	n/a		PRAC Recommendation - maintenance
IA/0052/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	24/08/2016	n/a		
IB/0053	C.I.11.z - Introduction of, or change(s) to, the	17/08/2016	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
R/0050	Renewal of the marketing authorisation.	26/05/2016	15/07/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Sprycel in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IAIN/0051	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2016	15/07/2016	SmPC and PL	
PSUSA/935/201506	Periodic Safety Update EU Single assessment - dasatinib	14/01/2016	n/a		PRAC Recommendation - maintenance
N/0049	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/10/2015	15/07/2016	PL	
IB/0048/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	14/10/2015	n/a		

	(excluding manufacturer for batch release) B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IG/0602	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	11/09/2015	n/a		
PSUV/0041	Periodic Safety Update	22/01/2015	19/03/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0041.
II/0045/G	This was an application for a group of variations. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	22/01/2015	n/a		
II/0043/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to	20/11/2014	19/03/2015	SmPC, Annex II and PL	

	new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0044/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	28/10/2014	n/a		
IB/0040/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.a - Change in batch size (including batch size	29/04/2014	n/a		

	ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				
PSUV/0038	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
IB/0039	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	13/01/2014	n/a		
II/0037	Update of section 4.6 of the SmPC to reflect the potential risk to the foetus when administered during pregnancy, further to a review of data on all pregnancies. Consequently, the RMP was updated accordingly. The contact details of the Dutch representative in the package leaflet have been updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	06/08/2014	SmPC and PL	Studies in animals have shown reproductive toxicity of dasatinib. Based on human experience, dasatinib is suspected to cause congenital malformations including neural tube defects, and harmful pharmacological effects on the foetus when administered during pregnancy. SPRYCEL should not be used during pregnancy unless the clinical condition of the woman requires treatment with dasatinib. If SPRYCEL is used during pregnancy, the patient must be informed of the potential risk to the foetus. Women of childbearing potential must be advised to use effective contraception during treatment.
II/0036	Update of sections 4.8 and 5.1 of the SmPC with 48-month follow-up data from study CA180056 in patients with newly diagnosed CML in the chronic phase (FU2 027.2). The package leaflet is updated accordingly. Furthermore, Annex II is also updated further to the re-classification of this post-	25/07/2013	06/08/2014	SmPC, Annex II and PL	As committed at the time of the approval of the indication of Sprycel for the treatment of adult patients with newly diagnosed chronic phase CML (EMEA/H/C/709/II/23), the Marketing Authorisation Holder (MAH) submitted results of the 48-month update of Study CA180056. The 48 months results from study CA180056 shows

	authorisation commitment as a condition to the Marketing Authorisation. The product information is also updated in line with the QRD template version 9.0 and the list of local representatives in the Package leaflet has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				continued high rates of cCCyR along with higher rates of MMR which are expected to translate into long term clinical benefit of dasatinib over imatinib. It is noted that the time to achieving a cCCyR and MMR was faster with dasatinib. Also, transformation to accelerated or blast phase occurred in fewer dasatinib-treated subjects compared with imatinib-treated subjects. As expected PFS and OS data remain immature. High rates of PFS and OS that were comparable across both treatment groups were observed, although fewer progressions were observed in the dasatinib group compared with the imatinib. The safety profile is still acceptable; it is manageable and comparable to that of imatinib. No new concerns have been identified with the 48 month follow up. The Summary of Product Characteristics has been updated to include the results of this 48-month update.
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IA/0034/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	07/12/2012	n/a		
II/0033	Update of section 5.3 of the SmPC with results from a new statistical evaluation of the tumour data of the	18/10/2012	19/11/2012	SmPC	In a two-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The

	2-year carcinogenicity study in rats. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				highest dose resulted in a plasma exposure (AUC) level generally equivalent to the human exposure at the recommended range of starting doses from 100 mg to 140 mg daily. A statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and of prostate adenoma in low-dose males was noted. The relevance of the findings from the rat carcinogenicity study for humans is not known.
II/0032	Update of sections 4.4, 4.8 and 5.1 of the SmPC with 36-month follow-up data from study CA180056 in patients with newly diagnosed CML in the chronic phase (FU2 027.1). The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	30/08/2012	SmPC and PL	As committed at the time of the approval of the indication of Sprycel for the treatment of adult patients with newly diagnosed chronic phase CML (EMEA/H/C/709/II/23), the Marketing Authorisation Holder (MAH) submitted results of the 36-month update of Study CA180056. Submission of the 36 months results from study CA180056 showed continued high rates of cCCyR along with higher rates of MMR which are expected to translate into long term clinical benefit of dasatinib over imatinib. It is noted that the time to achieving a cCCyR and MMR was faster with dasatinib. Also, transformation to accelerated or blast phase occurred in fewer dasatinib-treated subjects compared with imatinib-treated subjects. As expected PFS and OS data remain immature. High rates of PFS and OS that were comparable across both treatment groups were observed, although fewer progressions were observed in the dasatinib group compared with the imatinib. The safety profile is still acceptable; it is manageable and comparable to that of imatinib. No new concerns have been identified with the 36 month follow up. The MAH will continue to provide yearly updates in order to obtain longer follow-up in terms of overall survival.

					The Summary of Product Characteristics has been updated to include the results of this 36-month update.
II/0031	Update of sections 4.4, 4.8 and 5.1 of the SmPC further to the results of 5 years of follow-up of the dose optimisation study CA180034. The Package Leaflet has been updated accordingly and also to bring it in line with the SmPC with regards to adverse reactions with a frequency "uncommon" and "rare". C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC and PL	In this application, the MAH submitted the results of 5 years of follow-up of a dose optimisation study CA180034 in patients resistant or intolerant to imatinib that supported the approval of dasatinib at 100 mg QD in patients with chronic phase CML and at 140 mg QD in advanced disease CML and in Ph+ ALL. The results from this 5 year follow-up in CA180034 confirm the findings of earlier analyses that patients achieved clinical benefit on therapy with dasatinib. Treatment with 100 mg QD continues to provide efficacy similar to the initially approved dose of 70 mg BID. The safety analysis from CA180034 and the pooled safety analysis confirmed the tolerability of dasatinib. As a consequence, sections 4.4, 4.8 and 5.1 of the SmPC and the package leaflet have been udpated to reflect the findings from the 5 year update. The Package Leaflet was also updated to ensure that the information was consistent with section 4.8 of the SmPC with regards to adverse reactions with a frequency "uncommon" and "rare"
II/0030	Update of sections 4.4 and 5.1 of the SmPC with 24-month data of study CA180056 in patients with newly diagnosed CML in the chronic phase, further to the request of the CHMP following the assessment of FUM 027. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.1.	15/12/2011	20/01/2012	SmPC, Annex II, Labelling and PL	As committed at the time of the approval of the indication of Sprycel for the treatment of adult patients with newly diagnosed chronic phase CML (EMEA/H/C/709/II/23), the Marketing Authorisation Holder (MAH) submitted results of the 24-month update of Study CA180056. With the submission of the 24 month data the higher cCyR and MMR at 12 months achieved with dasatinib as compared to imatinib for first-line use has been confirmed

	C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation				and shows that the efficacy of dasatinib is maintained over time. The observed safety profile for dasatinib seen with the submitted 24 month data set was consistent with the known safety profile. The MAH will continue to provide yearly updates in order to obtain longer follow-up in terms of overall survival. The Summary of Product Characteristics has been updated to include the results of this 24-month update.
R/0028	Renewal of the marketing authorisation.	21/07/2011	29/09/2011	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Sprycel remains positive, but considers that its safety profile is to be closely monitored for the following reasons: - Sprycel has been approved based on surrogate efficacy endpoints and further surveillance of the mortality rate is required. - The additional issue of pulmonary arterial hypertension has been identified during the period covered by this renewal and requires updates of the product information and risk minimisation activities. - The CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the safety profile of Sprycel, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IB/0029	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a	19/06/2011	n/a	SmPC	The MAH applied to update section 5.3 of the SmPC as requested by the CHMP further to the assessment of the

	PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				results of a carcinocenicity study in rats (FUM 005). In addition, typographical errors were corrected in the German and Spanish annexes.
IA/0027	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	31/03/2011	n/a		
IA/0026/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD A.7 - Administrative change - Deletion of manufacturing sites	11/03/2011	n/a	Annex II and PL	
II/0023	Extension of indication of Sprycel in the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia in the chronic phase. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics and the Package Leaflet have been updated. Annex II has been updated to include the revised version number of the risk management plan (version 8.1). The MAH also took the opportunity to include the marketing authorisation numbers of recently approved 80 mg and 140 mg strengths in Annexes I and IIIA.	21/10/2010	06/12/2010	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Sprycel-H-709-II-23-AR.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0024	Update of SmPC section 4.5 with results from the final clinical study report CA180249 on the effect of omeprazole on the pharmacokinetics of dasatinib in healthy subjects. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	25/10/2010	SmPC	Study CA180249 was a Phase 1, open-label, single-sequence pharmacokinetic study conducted to assess the effect of omeprazole 40 mg on the pharmacokinetics of dasatinib in healthy subjects. A total of 14 subjects entered the study and received study medication. Thirteen (13) subjects completed the study. A single oral dose of 100 mg dasatinib was administered to subjects in the morning at approximately 9:00 a.m. on Days 1 and 6 in a fasted condition. Omeprazole was administered once daily in the morning at approximately 11:00 a.m. on Days 2 through 6 in a fasted condition. In a study of 14 healthy subjects, administration of a single 100 mg dose of Sprycel 22 hours following a 4-day, 40-mg omeprazole dose at steady state reduced the AUC of dasatinib by 43% and the Cmax of dasatinib by 42%. The recommendation that concurrent use of PPI and dasatinib is not recommended is still to be adhered to
X/0022	Additional strengths of 80 mg and 140 mg film-coated tablets. Annex I_2.(c) Change or addition of a new strength/potency	22/07/2010	30/09/2010	SmPC, Annex II, Labelling and PL	The goal of the MAH was to apply for the addition of two strengths of 80 mg and 140 mg of film-coated tablets. Sprycel 80 mg and 140 mg film-coated tablets contains the same active substance and excipients in the same proportional amounts as currently approved Sprycel 20 mg, 50 mg, 70 mg and 100 mg film-coated tablets. The new strengths (Sprycel film coated tablets 80 mg and 140 mg) are aimed to allow a reduced pill burden and support concordance with approved therapy. The 80 mg

					film coated tablet will allow patients to take the approved dose reduction of 80 mg QD in the case of neutropenia or thrombocytopenia and the 140 mg film coated tablet will allow patients to have flexibility of a one-unit daily dose, in line with the updated posology of a starting dose of 140 mg once daily for advance phase CML and Ph+ALL. This line extension application includes a waiver of the requirements to conduct an in vivo bioequivalence study (i.e., biowaiver) which was discussed and endorsed by the CHMP.
IA/0025	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	16/08/2010	n/a	Annex II	
II/0020	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and section 4 of the Package Leaflet further to a review of safety data from post-marketing experience and from 36-month follow-up safety data from long-term clinical studies. Section 5.1 of the SPC is also updated further to long-term follow-up study data. The Marketing Authorisation Holder also took the opportunity to make minor editorial and linguistic corrections to the SPC and to update the list of local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	05/05/2010	SmPC and PL	In this type II variation, the Marketing Authorisation Holder (MAH) provided up to 36 months of follow-up safety data in clinical studies. The results of updated analyses confirm initial findings of a dose of 100 mg QD in chronic phase CML and use of 140 mg QD in advanced phase CML and Ph+ALL. In updated analyses in the overall population of 2,182 dasatinib-treated subjects with up to 36 months of follow-up, no new safety signals were identified compared with analyses performed with 24 months of follow-up in this clinical trial population. In line with 36-month follow-up data from clinical trials, section 4.8 of the Summary of Product Characteristics (SPC) was updated to add "Hypoalbuminemia" as a rare event, to change the frequency of "Cholecystitis" from "rare" to "uncommon and to add "Genital swelling" under the footnote regarding "superficial oedema".

					In addition to the update from the studies, the safety data from the global marketed use of dasatinib included in the most recent Periodic Safety Update Report concludes that the safety profile of dasatinib remains similar to the profile established during clinical trials. However, the following adverse drug reactions reported during the post-marketing period have been added to section 4.8 of the SPC with a frequency "not known": atrial fibrillation/atrial flutter, thrombosis/embolism (including pulmonary embolism, deep vein thrombosis), interstitial lung disease, and fatal gastrointestinal haemorrhage. The Package Leaflet has been updated accordingly. Overall, review of the current data does not suggest that these post-marketing experiences have a clinically important impact that could change the risk-benefit profile of dasatinib. In addition, the following statement was included in section 5.1 of the SPC to reflect the efficacy results from the previously submitted 24-month follow-up data: "In patients with Ph+ ALL, the median duration of MaHR was 5 months and 12 months for the 140 mg once daily
IA/0021/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance	10/03/2010	n/a	Annex II	

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0019	To change the shelf life of the finished product as packaged for sale. IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	20/01/2010	n/a	SmPC	
IA/0018	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	20/08/2009	n/a		
II/0017	This type II variation concerns an update of sections 4.2, 4.4 and 5.2 of the SPC, upon request by the CHMP following the assessment of FUM 007, with information concerning patients with hepatic impairment and the results of the pharmacokinetic Study CA189951. In addition, the MAH took the opportunity to update the contact details for Estonia in the list of local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	28/07/2009	SmPC and PL	Based on the findings from Study CA189951, a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, due to the limitations of this clinical study, caution is recommended when administering Sprycel to patients with hepatic impairment. The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic-impaired subjects who received a 50 mg dose and 5 severely hepatic impaired subjects who received a 20 mg dose compared to matched healthy subjects who received a 70 mg dose of dasatinib. The mean Cmax and AUC of dasatinib adjusted for the 70 mg dose was decreased by 47% and 8%, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In severely hepatic-impaired subjects, the mean Cmax and AUC adjusted for the 70 mg

					dose was decreased by 43% and 28%, respectively, compared to subjects with normal hepatic function. Dasatinib and its metabolites are minimally excreted via the kidney.
II/0016	Update of Summary of Product Characteristics Update of Summary of Product Characteristics	25/06/2009	28/07/2009	SmPC	This type II variation concerns an update of the SPC, upon request by the CHMP following the assessment of PSU 22 (4th PSUR), to add information to sections 4.4 and 4.8 to reflect that in vitro and in vivo platelet assays suggest that Sprycel treatment may reversibly affect platelet activation, to add the ADR 'subdural haematoma' to section 4.8, and to make changes to the format of the presentation of safety data in section 4.8. Further, the MAH has implemented consequential editorial changes to the SPC.
II/0014	Update of Detailed Description of the Pharmacovigilance System Changes to QPPV Update of DDPS (Pharmacovigilance)	22/01/2009	26/02/2009	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS) in order to include a change of the Qualified Person for Pharmacovigilance (QPPV). In addition, the Marketing Authorisation Holder (MAH) took the opportunity to notify the CHMP of other minor changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated to include the new version number of the agreed DDPS.
II/0010	This type II variation concerns an update of sections 4.2, 4.4, 4.8, 4.9 and 5.1 of the SPC with 24-months follow-up data from two Phase 3 studies comparing the efficacy and safety of dasatinib administered once daily (QD) versus twice daily (BID) (current posology for the advanced phase CML and Ph+ALL indications) in subjects with chronic phase CML (CA180034) and advanced phase CML or Ph+ ALL	22/01/2009	26/02/2009	SmPC, Annex II and PL	Plese refer to the 'Scientific discussion' EMEA-H-C-709-II-10.

	(CA180035). The Package Leaflet has beeen amended accordingly. In addition, the MAH took the opportunity to provide an updated version of the RMP (version 6.0). Consequently, annex II has been updated to reflect the latest version agreed with the CHMP. Update of Summary of Product Characteristics and Package Leaflet				
IB/0015	IB_33_Minor change in the manufacture of the finished product	26/02/2009	n/a		
II/0012	Update of Summary of Product Characteristics	18/12/2008	10/02/2009	SmPC	This type II variation concerns an update of section 5.1 of the SPC, following the CHMP assessment of FU2 009.1, with results from the analyses of molecular response data after 24 months of follow-up at a dose of 70 mg dasatinib twice daily (BID) for advanced phase CML and Ph+ ALL patients from phase II studies CA180005, CA1800006 and CA180015. In patients with accelerated Phase CML, the rate of major molecular response (assessed in 41 patients with a CCyR) was 46% at 24 months. In patients with myeloid Blast Phase CML, the rate of major molecular response (assessed in 19 patients with a CCyR) was 68% at 24 months. The rate of major molecular response in patients with Lymphoid Blast Phase CML (all 22 treated patients with a CCyR) was 50% at 24 months, and in patients with Ph+ ALL the rate of major molecular response (all 25 treated patients with a CCyR) was 52% at 24 months.

II/0013	This type II variation concerns an update of section 5.3 of the SPC, upon request by the CHMP following the assessment of FUM 004, to include further information on in vivo phototoxicity based on the results of study DS 071387. Update of Summary of Product Characteristics	18/12/2008	29/01/2009	SmPC	Dasatinib was considered to be non phototoxic in vivo after a single oral administration to female hairless mice at exposures up to 3 fold the human exposure following administration of the recommended therapeutic dose (based on AUC).
II/0009	This type II variation concerned an update of section 5.3 of the SPC, upon request by the CHMP following the assessment of FUM 003 and FU2 003.1, with the results of an oral study of fertility and early embryonic development in rats (segment 1). In this study, dasatinib did not affect male or female fertility, but induced embryolethality at dose levels approximating human clinical exposures. In embryofoetal development studies, dasatinib likewise induced embryolethality with associated decreases in litter size in rats, as well as foetal skeletal alterations in both rats and rabbits. These effects occurred at doses that did not produce maternal toxicity, indicating that dasatinib is a selective reproductive toxicant from implantation through the completion of organogenesis. Update of Summary of Product Characteristics	20/11/2008	15/01/2009	SmPC and Annex II	In addition, the MAH took the opportunity to update annex IIB to reflect the latest version of the Risk Management Plan (version 4.0) agreed with the CHMP.
X/0007	The MAH applied for an additional strength of 100 mg of film-coated tablets. Annex I_2.(c) Change or addition of a new	23/10/2008	09/01/2009	SmPC, Annex II, Labelling and PL	The goal of the MAH was to apply for the addition of strength of 100 mg of film-coated tablets. Sprycel 100 mg film-coated tablets contains the same active substance and excipients in the same proportional amounts as currently

	strength/potency				approved Sprycel 20 mg, 50 mg and 70 mg film-coated tablets. The new strength (Sprycel film coated tablets 100 mg) is aimed to allow patients the flexibility and the convenience of a one-unit daily dose. Furthermore, this additional new strength supports an already approved posology, and is therefore not considered a significant change to the marketing authorisation. This line extension application includes a waiver of the requirements to conduct an in vivo bioequivalence study (i.e., biowaiver) which was discussed and endorsed by the CHMP.
IB/0011	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	13/11/2008	n/a	SmPC	
II/0008	Update of Summary of Product Characteristics, Annex II and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	22/07/2008	SmPC, Annex II and PL	The MAH applied for a type II variation to update sections 4.4, 4.8 and 5.1 of the SPC with 24-months follow-up data from phase II studies CA180005, CA180006, CA180013, CA180015 and CA180017. The Package Leaflet has been amended accordingly. Further, the Marketing Authorisation Holder (MAH) has updated annex IIB to include a reference to the Pharmacovigilance system (version 2.5) and the Risk Management Plan (version 3.0) agreed with the CHMP. In addition, the MAH have implemented some minor editorial changes in the SPC and annex II and took the opportunity to update the contact details of the local representative for Romania in the Package Leaflet. Please also refer to the Scientific discussion EMEA-H-C-709-II-08.

IB/0005	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	26/02/2008	n/a		
IA/0006	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	13/02/2008	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/11/2007	n/a	Annex II and PL	
IA/0003	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	20/11/2007	n/a	Annex II and PL	
II/0002	Update of sections 4.2, 4.4, 4.8, 4.9 and 5.1 of the SPC in line with the first results at 6 months of follow-up of the ongoing studies CA180034 and CA 180035. Furthermore, the MAH took the opportunity to update section 4.8 of the SPC in line with the outcome of the CHMP assessment of the 1st PSUR and according to MedDRA version 8.2. The Package Leaflet has been amended accordingly. In addition, the MAH has implemented some minor editorial changes in the annexes and updated the contact details of the local representatives for Romania and Denmark in the Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/07/2007	22/08/2007	SmPC, Labelling and PL	Please refer to the Scientific discussion EMEA-H-C-709-II-02.
N/0001	Minor change in labelling or package leaflet not	15/02/2007	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				